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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/713,653 | 11/14/2003 | Molly Accola | FORS-08453 | 1634 |

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| EXAMINER | |
|---|---|
| GOLDBERG, JEANINE ANNE | |
| **ART UNIT** | **PAPER NUMBER** |
| 1634 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/713,653 | ACCOLA ET AL. | |
| | Examiner | Art Unit | |
| | Jeanine A. Goldberg | 1634 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *03 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☐ Claim(s) *28,30-33,36-40,43,44 and 47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *28, 30-33, 36-40, 43-44, 47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

1. This action is in response to the papers filed October 3, 2007. Currently, claims 28, 30-33, 36-40, 43-44, 47 are pending.

2. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

3. This action is **FINAL.**

4. Any objections and rejections not reiterated below are hereby withdrawn.

a. The 102 rejections have been withdrawn in view of the amendments to the claims to require several dependant claims into the independent claim.

b. The 103 rejection of Hsu, Fors, CFMDB and Hall has been withdrawn in view of the amendments to require deletion mutations.

### *Election/Restrictions*

5. Applicant's election without traverse of Group II, Claims 28-35 and newly added Claims 36-47 in the paper filed August 21, 2006 is acknowledged.

The requirement is still deemed proper and is therefore made FINAL.

### *Priority*

6. This application claims priority to several provisional applications and as a CIP of 10/371,913, filed February 21, 2003.

### *Drawings*

7. The drawings are acceptable.

### ***New Grounds of Rejection Necessitated by Amendment***

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 28, 30-33, 36-40, 43-44, 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ohnishi et al. (J. Hum. Genet. Vol 46, pages 471-477, 2001) in view of The Cystic Fibrosis Mutation Database (http://www.genet.sickkids.on.ca/cftr/app) and Fors et al. (Pharmacogenomics, Vol. 1, No. 2, pages 219-229, 2000), Mein et al. (Genome Research, Vol. 10, pages 330-343, 2000) and Hall (PNAS, Vol. 97, No. 15, pages 8272-8277, July 2000).

Ohnishi et al. teaches a high-throughput SNP typing system for genome-wide association studies. Ohnishi teaches combining Invader assay with multiplex PCR (abstract). Ohnishi teaches amplifying 100 genomic DNA fragments in a single tube and analyzed each SNP with the Invader assay. Ohnishi teaches that the results indicate the feasibility of undertaking genome-wide association studies using blood samples of only 5-10ml (abstract). Ohnishi teaches that primers were designed, multiplex amplifications were performed and PCR was performed for 35 cycles. Ohnishi teaches that after amplification was performed using 50ng of genomic DNA, the Invader assay was performed with unique probes corresponding to each SNP allele (page 472, col. 2). Ohnishi teaches that a set of 24 SNP loci was performed and the sequencing results were 100% identical to the genotyping data obtained by the Invader assays. Ohnishi teaches numerous benefits of multiplex anlaysis including reduced cost, significant reduction in the amount of genomic DNA required and savings in time (page 474, col. 1-2).

Ohnishi does not specifically teach amplifying nucleic acid with less than 25 cycles and using 20 CFTR alleles for analysis of SNPs and deletions.

However, the cystic fibrosis mutation databases teaches the collection of mutations in the CFTR gene. There are currently **1542** mutations listed in this CFTR mutation database. The mutations include SNPs and deletions. The most common F508 mutation is a deletion.

Moreover, Fors teaches large-scale SNP scoring from unamplified genomic DNA. Fors teaches the Invader assay offers a simple diagnostic platform to detect single nucleotide changes with high specificity and sensitivity from unamplified, genomic DNA. The Invader assay uses a structure-specific 5' nuclease (or flap endonuclease) to cleave sequence-specific structures in each of two cascading reactions. The cleavage structure forms when two synthetic oligonucleotide probes hybridize in tandem to a target. Fors teaches that the signal amplification permits identification of single base changes directly from genomic DNA without prior amplification (abstract). The Invader technology is in routine use today for high-throughput SNP screening. The technology involves a simple, cascading reaction that can detect mutations and SNPs directly from unamplified genomic DNA or RNA in a homogeneous, isothermal, FRET-based format (page 222). Figure 1 illustrates the schematic of the Invader assay which contains various oligonucleotides including an oligonucleotide which comprises various 5' and 3' positions that do not hybridize to target sequences. The technology is readily adapted to different sequences since the unlabeled analyte-specific oligonucleotides used in the primary reaction; no new dye-labeled oligonucleotides are needed (page 223, col. 1). This creates a streamlined approach to creating new assays allows rapid and accurate synthesis, purification and quantification of new SNP assay sets.

Similarly, Mein teaches evaluating SNPs and an insertion deletion polymorphisms using PCR with Invader. Mein further teaches the benefits of automating the assay for savings on labor costs.

Further, Hall specifically teaches that PCR is indispensable too in molecular biology but the use of exponential target amplification creates the possibility of amplicon cross-contamination, makes quantitative analysis complicated and reduces the specificity with which small genetic variations can be detected (page 8276, col. 2).

Therefore, it would have been prima facie obvious at the time the invention was made to generate a multiplex method, as taught by Ohnishi, for Cystic Fibrosis SNPs and deletions, as taught by CFMXB, using the PCR Invader technology design of Fors and Mein with less than 25 cycles, as taught by Hall. The ordinary artisan would have been motivated to have applied the PCR-Invader assay to CFTR gene SNPs and deletion mutations because CFTR gene mutations are diagnostic of Cystic fibrosis which is a debilitating disease. The art clearly illustrates the ability of Invader to detect both SNPs and deletion mutations. Moreover, Ohnishi specifically teaches the benefits of the PCR-invader assay as allowing multiplex analysis with the expected benefits of saving time, sample and cost. Thus, detecting multiple mutations simultaneously, including over 30 mutations, would have been obvious at the time the invention was made given the number or CF mutations in the CFTR gene.

The ordinary artisan would have been motivated to have used 17 cycles or fewer to avoid the well known art difficulties of PCR amplification taught by Hall. Although Ohnishi suggests the use of 35 cycles for PCR amplification, the skilled artisan, given

the teachings of Hall would have appreciated that exponential amplification introduces possibilities of amplicon cross contamination. As noted in *In re Aller*, 105 USPQ 233 at 235, "More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.". Routine optimization is not considered inventive and no evidence has been presented that the selection of cycling performed was other than routine, that the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art. The prior art teaches the ability to perform Invader assays with no prior target amplification (see Fors) and Ohnishi teaches using 35 cycles. Thus, using an intermediate number of cycles, namely 25, 20 or 17 cycles would constitute routine optimization in the art.

***Conclusion***

**10. No claims allowable over the art.**

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

J. Goldberg

**Jeanine Goldberg**
**Primary Examiner**
November 27, 2007